Response

Claims 94-110, 112-113, and 115-116 are currently pending and under examination. Claims 94, 96, 98, 100, 101, 107-109, and 112 are amended as shown. Claims 95 and 99 are cancelled and the subject matter combined into claims 94 and 98, respectively. Support for the "Ki characteristic of NHE-1 antiport blockers from 0.068 ±0.002 to 0.25 ±0.02 μM" in claims 94 and 108, and also in claims 96 and 112, is found at least in Table 5 and page 31 and 32. The reference to the upper magnitude of the Ki value not being "higher than" the defined Ki is supported at page 15, paragraph 1 and by the limitations cited in Table 5. The cited values are representative of the class of amiloride analogues that effectively inhibit NHE-1, including the other analogues listed in Table 5. For example, ethyl-isopropyl-amiloride (EIPA) Ki = 0.068 ±0.002 μM), dimethylamiloride (DMA) (Ki = 0.15 μM; see L'Allemain *et al.*, *J Biol Chem.* 259(7):4313-9 (1984)), HOE694 (Ki = 0.16 μM; see Counillon *et al.*, 1993 reference cited with Table 5), methylpropylamiloride (Ki = 0.08 μM; see Counillon *et al.*, 1993 reference cited with Table 5), and cariporide (Ki = 0.25 ±0.02 μM).

The term "NHE-1 antiport blocker" in claims 94 and 108 is changed to "NHE-1 antiport inhibitors" for consistency with the other claims. The term "sufficient to" was found in the original claims at the filing of this application, and is defined within the claim by the stated action. The term "amiloride analogue" in claims 96 and 112 is defined as a limited class of compositions within a stated range of Ki values, thereby numerically defining the "analogue" so that is not an indefinite term, and further distinguishing the composition from amiloride itself. The dependency of claim 100 is changed to reflect the cancellation of claim 99, and its combination into claim 98. "NHE" is changed to "NHE-1" throughout for consistency.

No new terms or new matter is added to any claim.

Response to Rejection of Claim 101 under 35 U.S.C. § 112, first paragraph.

The Examiner has rejected claim 101 under 35 U.S.C. §112, first paragraph, under the written description requirement regarding latanoprost as a representative member of the class of compositions precursor prostaglandins. However, to advance the case, without necessarily agreeing with the Examiner's arguments, in light of the present amendment, the

rejection is moot. Accordingly, Applicants respectfully request reconsideration and allowance of the claim.

Response to Rejection of Claims 94-104, 107-110, 112, 113, 115 and 116 under 35 U.S.C. § 112, first paragraph.

The Examiner has rejected claims 94-104, 107-110, 112, 113, 115 and 116 under 35 U.S.C. §112, first paragraph, under the written description requirement regarding use of the term "selectively." However, to advance the case, rather than argue the propriety of the term "selectively," although "selective inhibition at very low concentrations" is well supported in the specification, Applicants have amended claims 94 and 108, and hence the claims dependent thereon, by removing the term "selectively" and instead providing numerical values of Ki against the NHE-1 from Table 5. In light of the present amendment, therefore, the rejection is moot. Accordingly, Applicants respectfully request reconsideration and allowance of claims 94-104, 107-110, 112, 113, 115 and 116.

Response to Claim Rejection under 35 U.S.C. § 112, second paragraph.

The Examiner has rejected claim 113 under 35 U.S.C. §112, second paragraph, as indefinite regarding antecedent basis for the dependency on claim 112. In light of the present amendment limiting the "amiloride analogues" that may be applied in claim 112 to only an established and limited class, the rejection is moot. Antecedent basis is, therefore, provided for claim 113. Accordingly, Applicants respectfully request reconsideration and allowance of claim 113.

Response to First Rejection under 35 U.S.C. §102(b) over Cherksey

The Examiner has maintained the previous rejection of claims 94-96, 102 and 107 under 35 U.S.C. §102(b) as anticipated by Cherksey (US Patent No. 4,950,591). In making this rejection, the Examiner still relies upon Cherksey for the teaching that amiloride is an agent that "blocks ion transport and interacts with a Sodium-Hydrogen Exchange inhibitor," and that amiloride and amiloride derivatives are capable of regulating membrane transport, cellular volume and other cellular pressure disorders. See columns 1-3. This conclusion is incorrect, and Applicants reiterate all arguments of record regarding the Cherksey reference. Cherksey does not actually teach any interaction with a "sodium-hydrogen exchange inhibitor," nor is the amiloride gel utilized by Cherksey at pH 4.5

suitable for actual administration to the eye. Without evidence that Cherksey's gel would necessarily operate as Applicants' inhibition of NHE-1 antiport activity at the Ki values indicated, such a selective effect is not, and cannot be assumed to be, inherent in the Cherksey reference.

The sodium channel is not the same as or equivalent to the sodium-hydrogen antiport. The sodium channel and the sodium-hydrogen antiports, as explained above – are not even found in the same regions of the epithelial cells of the eye. While Cherksey claims the use of amiloride solely for the use of the isolated peptide as a diagnostic and experimental tool, by comparison, Applicants' invention neither teaches, nor claims, a method for regulating the "sodium channel" or its role in aqueous humor formation. Cherksey teaches only the use of amiloride per se, without mention of the limited range of amiloride analogues used in Applicants' invention.

Furthermore, Cherksey simply refers to sodium channels in the eye without taking account of their location. The amiloride-sensitive sodium channel has been found expressed in the nonpigmented ciliary epithelial cells, which are closest to the aqueous humor. See Civan *et al.*, "Potential contribution of epithelial Na+ channel to net secretion of aqueous humor," *J. Exp. Zool.* 279:498-503 (1997), believed to be of record. If the article cannot be located, Applicants will certainly provide it to the Examiner if so requested.

This raises the possibility that the amiloride-sensitive sodium channels participate in the reabsorption of aqueous humor, slowing the rate of net aqueous humor inflow. By definition, therefore, this means that the Cherksey teachings fall outside of Applicants' invention.

In fact, Cherksey teaches that blocking the sodium channel of the nonpigmented ciliary epithelial cells with amiloride *increases* inflow, *resulting in increased intraocular pressure* – which is contrary to the clinical intent of Applicants' invention. On the basis of that information, a knowledgeable practitioner would be led to *stimulate* the NPE sodium channels; not block them, and further demonstrates that Cherksey's invention to determine the effect of amiloride on the sodium channels, would have had no effect, particularly at the concentrations used by Cherksey, on the sodium-hydrogen antiports that are selectively inhibited by Applicants' claimed method. Thus, Cherksey not only fails to anticipate

Applicants' invention, it actually leads one away from what is taught by Applicants' patent application regarding regulation of the antiports.

Cherksey neither mentions, nor suggests, that inhibiting or blocking NHE exchange would reduce aqueous humor inflow or intraocular pressure. Thus, although Cherksey, as a valid patent, may be admitted for all that it teaches - it can at best be considered valid only for the use of "amiloride" per se, but not for unknown or undefined amiloride analogues having completely different activity and Ki values for NHE-1 inhibition than that which is defined for amiloride itself. Cherksey's amiloride effect is taught only with regard to the sodium channels. Even a patent reference cannot be considered valid for that which it fails to encompass.

The established Ki of amiloride is 3.9 ±0.2 (see Table 5 of Applicants' specification), which is more than 10-fold higher than the range of Ki values utilized in Applicants' invention. See claims 94, 96, 108 and 112 which limit the NHE-1 antiport inhibitors to a Ki no greater than 0.25 ±0.02 μM. Consequently, the "amiloride" per se utilized by Cherksey is not, and cannot be encompassed within or anticipate the defined amiloride analogues used in Applicants' invention because the weak potency of amiloride itself if applied as an NHE inhibitor caused the Ki to be so high that it is 10-fold higher than the Ki of the highest of Applicants' inhibitor analogues.

Contrary to the Examiner's argument, Cherksey does not teach applying amiloride to the nonpigmented ciliary epithelial cells, and certainly never teaches the use of any "amiloride derivative" for which the Ki falls within the defined range of Applicants' amiloride analogues. Moreover, Cherksey never teaches the use of an NHE-1 antiport inhibitor having a Ki no greater than 0.25 ±0.02 μM.

Accordingly, Cherksey fails to anticipate each and every element of Applicants' claimed invention - which requires the administration of an NHE-1 inhibitor displaying an inhibitor constant (Ki) characteristic of NHE-1 antiport inhibitors, "from 0.068 ±0.002 to 0.25 ±0.02 μM." Moreover, specifically Cherksey could not anticipate claims 98 and 112, wherein the NHE-1 inhibitor is an "amiloride analogue for which the Ki against NHE-1 antiport does not exceed 0.25 ±0.02 μM." As a result, the Cherksey reference fails to anticipate Applicants' present invention in that Cherksey failed to use or suggest the defined NHE-1 inhibitors taught in Applicants' invention.

Applicants ask that in light of the arguments and evidence of record, and of the amended claims, the rejection of Applicants' claims under 35 U.S.C. §102(b) over Cherksey be reconsidered and withdrawn, and that claims 94, 96, 102 and 107 be moved to allowance.

Response to Second Rejection under 35 U.S.C. §102(b) over Drug Facts and Comparisons

The Examiner has maintained the rejection of claims 94 and 101-104 under 35 U.S.C. §102(b) as being unpatentable under "Drug Facts and Comparisons" (1994). In making this rejection, the Examiner relies upon "Drug Facts and Comparisons" for teaching the use of timolol, which the Examiner defines as a beta blocker in reliance on the prior art and on Applicants' list at page 6, lines 23-26. However, as previously shown on the record, by cited prior art and by Declaration in Applicants' prior Response dated November 10, 2005, timolol was not recognized by those knowledgeable in the field to be a sodium-hydrogen exchange (NHE) inhibitor.

Regardless of the Examiner's arguments that reduction of intraocular pressure is demonstrated by the use of timolol in "Drug Facts and Comparisons," the reference offers no evidence that timolol achieved any inhibition of sodium-hydrogen antiport activity *in the ciliary epithelial cells*.

Applicants not only "administer" a pharmaceutical composition in their claimed method, the composition is expressly an NHE-1 inhibitor that displays "an inhibitor constant (Ki) characteristic of NHE-1 antiport inhibitors, from 0.068 ±0.002 to 0.25 ±0.02 μM." In the absence of any direct scientific evidence that timolol directly binds to the NHE-1 exchanger, the Ki for timolol has not been determined, and as a result, timolol is not encompassed within the subject matter of claim 94. If timolol is not included within claim 94, or any claim dependent thereon, it is therefore excluded from Applicants' claims to the present invention, meaning that because "Drug Facts and Comparisons" is limited to the use of timolol, the cited reference is irrelevant to Applicants' claimed invention.

Inherency is not a factor in the "Drug Facts and Comparisons" reported reduction of intraocular pressure in the subject animal in conjunction specifically with their treatment with timolol, as compared with Applicants' claimed invention. The cited reference offers no suggestion that intraocular pressure was tested by the authors of "Drug Facts and

Comparisons." But that is irrelevant given that Applicants' claims do not encompass timolol, because Applicants' NHE-1 antiport inhibitors must display a Ki from 0.068 ±0.002 to 0.25 ±0.02 μM. No evidence places timolol within that range for NHE-1 inhibition. Inherency cannot be assumed without some level of evidence or support, yet none is offered to place timolol within Applicants' NHE-1 inhibitor compositions. See, e.g., *Verdegaal Brothers, Inc. v. Union Oil Co. of Calif.*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987) ("Inherency may not be established by probabilities or possibilities. The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient.).

Only Applicants' own invention teaches the method of reducing secretion of aqueous humor by therapeutically inhibiting NHE-1 antiport activity in the ciliary epithelial cells of the eye of a subject by therapeutically administering to the cells a modulating amount of an NHE-1 inhibitor sufficient to inhibit cellular antiport activity, the NHE-1 inhibitor to selectively inhibit cellular antiport activity, the NHE-1 inhibitor displaying an inhibitor constant (Ki) characteristic of NHE-1 antiport inhibitors, from 0.068 ±0.002 to 0.25 ±0.02 μM; thereby, regulating salt uptake or release in aqueous humor formation; and reducing net inflow. Any ß-blockers referenced by the Examiner must also fall within the stated Ki of Applicants' claimed invention - or they are not encompassed within the claimed subject matter. The teaching of a cited reference is of no effect on the patentability of the claims set forth in a patent application, unless the reference teaches what is specified in the claims of the application used to define the invention. "Drug Facts and Comparisons" offers no equivalent or inherent therapeutic method to Applicants' expressly claimed invention, nor in fact, does the reference teach any therapeutic method at all, offering only prophylaxis.

Consequently since each and every element of Applicants' claims 94 and 101-104 are neither expressly stated nor inherently described in a single prior art reference, Applicants' claims are not anticipated by the "Drug Facts and Comparisons" reference under 35 U.S.C. § 102(b). As a result, Applicants ask that in light of the claim amendments, the arguments of record and the foregoing arguments, the rejection under 35 U.S.C. § 102(b) over "Drug Facts and Comparisons" be reconsidered and withdrawn, and claims 94 and 101-104 be moved to allowance.

Response to Rejections under 35 U.S.C. §103(a) over Adorante and Cherksey

The Examiner has maintained the rejection of claims 94-96, and 99-104, 107–110, 112, and 113 under 35 U.S.C. §103(a) as unpatentable over Adorante (US Patent No. 5,559,151) and Cherksey (US Patent No. 4,950,591). In making this rejection, the Examiner relies on Adorante for the use of 4,4'-diisothiocyanato-stilbene-2,2'-disulfonate (DIDS) to treat glaucoma and/or ocular hypertension, although the Examiner agrees that Adorante fails to suggest co-administration of NHE/NHE-1 inhibitors. However, the Examiner further combines Cherksey with Adorante for the teaching that amiloride blocks ion transport and interacts with a sodium-hydrogen exchange inhibitor and that amiloride and amiloride derivatives are capable of regulating membrane transport, cellular volume and other cellular pressure disorders. The Examiner's conclusion is based on the premise that it would have been obvious to "employ two agents well known to treat glaucoma/ ocular hypertension together to treat the very same condition." However, Applicants refute the Examiner's conclusion.

Applicants agree with the Examiner that Adorante fails to suggest co-administration of NHE/NHE-1 inhibitors. Therefore, to provide obviousness, the combined Adorante + Cherksey reference must teach each and every element of Applicants' claimed invention. Given that Adorante offers no NHE-1 inhibitor required in Applicants' claims, that element of the combined reference must be provided by Cherksey. However, Applicants rely upon the above reasons as applied under 102(b) as to why Cherksey does not and cannot teach more than what is stated in the patent – which is the use of amiloride – which is also for the above-stated reasons not an NHE-1 inhibitor within Applicants' claims. Cherksey offers no suggestion or reference to any amiloride analogue displaying "an inhibitor constant (Ki) characteristic of NHE-1 antiport inhibitors, from 0.068 ±0.002 to 0.25 ±0.02 μM," and certainly not an NHE-1 inhibitor for which the Ki does not exceed 0.25 ±0.02 μM. Instead, Cherksey uses amiloride itself, for which the Ki is more than 10-fold higher for NHE-1 inhibition than that which is found in the defined *amiloride analogues* used and claimed by Applicants. As a result, the Cherksey reference, even when added to Adorante, cannot render Applicants' invention obvious because Cherksey failed to use or suggest the defined NHE-1 inhibitors taught in Applicants' invention.

Since the combined Adorante/Cherksey references fail to teach administering NHE-1 inhibitors to the antiports to regulate antiport activity by selectively inhibiting sodium-proton exchange – as it is expressly claimed by Applicants - the combined references cannot render Applicants' invention obvious. Even when combined, the cited references fail to teach each and every element of Applicants' claimed invention. Accordingly, Applicants respectfully request that the rejection of claims 94-96, 99-104, 107-110, 112, 113 under 35 U.S.C. §103(a) be reconsidered and reversed, and that the claims be moved to allowance.

Response to Rejections of Claims 94-98, 102-104, 107-110, 112, 113 and 115, and to the separate rejection of claim 116 under 35 U.S.C. §103(a) over Brandt and Cherksey

The Examiner has rejected claims 94-98, 102-104, 107-110, 112, 113 and 115, as well as in the separate rejection of claim 116, under 35 U.S.C. §103(a) as unpatentable over Brandt (US Patent No. 5,559,151) and Cherksey (US Patent No. 4,950,591).

In making this rejection, the Examiner relies on Brandt for the use of an inhibitor of a Na^+-K^+-$2Cl^-$ (symport), such as bumetanide, to treat glaucoma and/or ocular hypertension, although the Examiner agrees that Brandt fails to suggest co-administration of NHE/NHE-1 inhibitors. However, the Examiner further combines Cherksey with Brandt for the teaching that amiloride blocks ion transport and interacts with a sodium-hydrogen exchange inhibitor, and that amiloride and amiloride derivatives are capable of regulating membrane transport, cellular volume and other cellular pressure disorders. The Examiner's conclusion is based on the premise that it would have been obvious to "employ two agents well known to treat glaucoma/ocular hypertension together to treat the very same condition." Applicants, however, refute the Examiner's conclusion.

Applicants agree with the Examiner that Adorante fails to suggest co-administration of NHE/NHE-1 inhibitors. Therefore, to provide obviousness, the combined Brandt + Cherksey reference must teach each and every element of Applicants' claimed invention. Given that Brandt offers no NHE-1 inhibitor required in Applicants' claims, that element of the combined reference must be provided by Cherksey. However, Applicants rely upon the above reasons as applied under 102(b) as to why Cherksey does not and cannot teach more than what is stated in the patent – which is the use of amiloride – which is also for the above-stated reasons not an NHE-1 inhibitor within Applicants'

claims. Cherksey offers no suggestion or reference to any amiloride analogue displaying "an inhibitor constant (Ki) characteristic of NHE-1 antiport inhibitors, from 0.068 ±0.002 to 0.25 ±0.02 μM," and certainly not an NHE-1 inhibitor for which the Ki does not exceed 0.25 ±0.02 μM. Instead, Cherksey uses amiloride itself, for which the Ki is more than 10-fold higher for NHE-1 inhibition than that which is found in the defined *amiloride analogues* used and claimed by Applicants. As a result, the Cherksey reference, even when added to Adorante, cannot render Applicants' invention obvious because Cherksey failed to use or suggest the defined NHE-1 inhibitors taught in Applicants' invention.

In addition, Brandt's patent teaches the administration of bumetanide alone, *without the presence of an anion exchanger isoform 2 (AE2).* See, Applicants' claim 98 with regard to inhibition of the Na^+-K^+-$2Cl^-$ symports, wherein when bumetanide is used, it must be "administered in combination with an anion exchanger isoform 2 (AE2)."

Dr. Civan and others have demonstrated that bumetanide alone, as used by Brandt, is ineffective in lowering IOP *in vivo*. See, references of record, *i.e.*, Gabelt *et al.* "Anterior segment physiology after bumetanide inhibition of Na-K-Cl cotransport," *Invest. Ophthalmol. Vis. Sci.* 38:1700-7 (1997)(demonstrating that bumetanide had no effect on IOP of live monkeys). Subsequently, Dr. Civan and associates demonstrated that bumetanide also has no effect on IOP of the live mouse, and it lowers IOP only if the sodium-proton exchange is also blocked (see, 2002 Avila *et al.*, reference in *Invest. Ophthalmol. Vis. Sci.* 43:1897-1902) of record.

Thus, Brandt has no relevance to Applicants' claimed method of selectively blocking of sodium-proton exchange, as confirmed by the Examiner's acknowledgement that Brandt "fails to suggest administration of selective NHE/NHE-1 inhibitors." Linking treatment of bumetanide as an inhibitor of a Na^+-K^+-$2Cl^-$ (symport) (Brandt) with amiloride in a gel to block the ENaC sodium channel (Cherksey) would in no way lead one of skill in the art to believe that the combined teaching could selectively block sodium-proton exchange (since that is not mentioned or suggested by either component of the combined art), in order to reduce net inflow at the sodium-hydrogen antiports within the ciliary epithelial cell layer. Cherksey offers no suggestion or reference to any amiloride analogue displaying "an inhibitor constant (Ki) characteristic of NHE-1 antiport inhibitors, from 0.068 ±0.002 to 0.25 ±0.02 μM," and certainly not an NHE-1 inhibitor for which the

Ki does not exceed 0.25 ±0.02 μM. Instead, Cherksey uses amiloride itself, for which the Ki is more than 10-fold higher for NHE-1 inhibition than that which is found in the defined *amiloride analogues* used and claimed by Applicants. As a result, the Cherksey reference, even when added to Brandt, cannot render Applicants' invention obvious because Cherksey failed to use or suggest the defined NHE-1 inhibitors taught in Applicants' invention.

As a result, when the cited references are combined as proposed, the combination fails to teach each and every element of Applicants' claimed invention. Of course, as above, inherency does not apply to the combined references. See, *Jones v. Hardy* 220 USPQ 1020, 1025 (Fed. Cir. 1984) (The fact that a claimed invention is based on an inherent quality of a product well known in the art does not mean the invention is obvious, as this confuses anticipation by inherency with obviousness). Since for the above-stated reasons, Cherksey fails to teach administering an NHE-1 inhibitor (as defined in Applicants' claimed invention) to the antiports, as taught for the first time by Applicants, Cherksey cannot supplement the gap left by Brandt. Neither teaches a method for therapeutically reducing net inflow by inhibiting sodium-hydrogen antiport activity in the eye of a human or animal subject in need of antiport regulation to reduce intraocular pressure in accordance with Applicants' claimed invention. Consequently, the combination of Brandt and Cherksey still fails to render Applicants' invention obvious. Accordingly, Applicants respectfully request that the rejection of claims 94-98, 102-104, 107-110, 112, 113 and 115, as well as that the separate rejection of claim 116, under 35 U.S.C. §103(a) be reconsidered and reversed, and that the claims be moved to allowance.

In sum, therefore, Applicants believe that all rejections have been overcome, and the application is in condition for allowance. Accordingly, Applicants respectfully ask that the application be moved to allowance at the earliest date possible. Should the Examiner have any questions or comments regarding Applicants' amendment or response, please contact Applicants' undersigned representative at (215) 772-7550. Please direct all correspondence to the below-listed address. If there are any fees due in connection with the filing of this response, please charge the fees to Deposit Account No. 50-4764.

Respectfully submitted,
Civan *et al.*

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